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Topical Review

Propofol for sedation in the intensive care unit: essentials for the clinician

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Propofol is a short-acting intravenous anesthetic commonly utilised in the intensive care unit (ICU) for sedation of mechanically ventilated patients. The rapid onset and termination of action make it an attractive drug for use in the ICU. The safety profile of propofol is well established. However, there are potential adverse reactions associated with the drug. This review discusses the pharmacology, administration and adverse effects associated with propofol with which clinicians who administer propofol should be familiar.

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Propofol (Diprivan, Zeneca Pharmaceuticals, Wilmington, DE, U.S.A.) is an intravenous sedative-hypnotic recently approved by the Food and Drug Administration for sedation of mechanically ventilated patients in the intensive care unit (ICU) (1–3). Propofol has been utilised for many years as an anesthetic agent for surgical procedures. However, the drug remains unfamiliar to many ICU personnel. Many features of propofol make it attractive for short-term use (less than 5 days) in the general ICU setting: rapid onset of action, short duration of clinical effect, ease of titration, rapid cessation of effect, limited accumulation of the parent compound or metabolites, and minimal adverse effects (4–6). Propofol differs from other sedatives commonly utilised in the ICU, such as benzodiazepines and opiates, in chemical structure, sedative properties and side-effect profile. All practitioners who care for the critically ill should be familiar with the basic clinical indications, pharmacology, administration and potential adverse effects associated with propofol.

Indications

Propofol has been utilised for many types of surgical procedures, including cardiovascular, ophthalmic and neurosurgical, as well as a variety of outpatient surgical procedures. Other clinical situations in which propofol has been utilised include conscious sedation, electroconvulsive therapy (7), cardioversion, tracheal intubation (8,9) and mechanical ventilation (10). There have been reports of the efficacy of propofol for chemotherapy-induced emesis (11), as well as an antipruritic in patients with intractable pruritis due to liver disease (12). Propofol has also been utilised effectively to treat status epilepticus (13) as well as tetanus (14). Table 1 displays some of the non-surgical clinical indications of propofol.

Clinical Pharmacology

Propofol (2,6-diisopropylphenol) is an alkyl phenol derivative that possesses sedative and hypnotic properties. The drug has little water solubility and, therefore, is formulated in an oil-in-water emulsion consisting of 1·0% propofol, 10% soybean oil, 2·25% glycerol and 1·2% egg phosphatide. The drug is contraindicated in patients with hypersensitivity to eggs (4,6). Propofol possesses very little analgesic properties and is unrelated to opioids, benzodiazepines and tranquilizers. Propofol usually produces hypnosis within 1 min of intravenous administration, the approximate time for one arm-brain circulation to occur (4).

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TABLE 1. Non-surgical uses of propofol

Tracheal intubation
Mechanical ventilation
Bronchoscopy
Cardioversion
Electroconvulsive therapy
Chemotherapy associated emesis
Liver disease induced pruritis
Status epilepticus
Tetanus

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

Pharmacokinetics describes the rate and extent of drug handling by the body, namely absorption, distribution, metabolism and excretion. Pharmacodynamics describes the pharmacologic responses the drug has on the body (6,16,17). The pharmacokinetic profile of propofol is characterised by its rapid tissue distribution from the blood and rapid clearance (15). Propofol is extremely lipophilic which accounts for its rapid distribution to highly perfused tissues as heart, lung, brain and liver (6). The half-life of propofol is approximately 1·8–4·1 min (18). The rapid tissue distribution and short half-life account for the drug's rapid onset and short duration of action. After cessation of infusion, blood concentrations decline swiftly, with an average decrease of 50% in 10 min. Clinically, this accounts for rapid recovery times in most patients once the drug is discontinued (10–30 min); however, after prolonged infusions, the terminal half-life may increase to 3 days (4). The volume of distribution of propofol is between 209 and 1008 l kg^{-1}, due to its lipophilic nature. Approximately 98% of propofol is plasma-protein bound and is mainly hepatically metabolised to produce inactive water-soluble sulfate and glucuronide conjugates that are excreted in the urine (6,19). Less than 0·3% of a dose is excreted in the urine and feces as the parent compound (4,15). There is no significant change in pharmacokinetics in patients with chronic liver disease or chronic renal failure, making dosing adjustments unnecessary in these groups of patients. However, age does affect the kinetics of propofol, with elderly patients having a lower clearance rate than younger cohorts, reflecting the reduction in cardiac output and hepatic blood flow that occurs with aging (20,21). Hence, recommended dosages are lower in the elderly.

The most clinically significant pharmacodynamic properties of propofol are referable to the neurologic, cardiovascular and respiratory systems. Propofol produces rapid hypnosis and has synergistic activity when administered concurrently with barbiturates, benzodiazepines and opioids. The drug has anticonvulsant activity which is likely mediated by γ-aminobutyric acid (GABA) receptors in the brain (15). Propofol decreases cerebral blood flow by up to 50% with a concurrent decrease in intracranial pressure. Cerebral autoregulation, however, is preserved during propofol infusion (4). Cerebral metabolic oxygen requirements also decrease by 18–36% (22).

The main effect of propofol on the cardiovascular system is hypotension, which results primarily from a reduction in systemic vascular resistance (10,21). Reduction of systolic blood pressure by 30% of baseline values occurs in up to 26% of ICU patients. Propofol may also directly decrease cardiac output by depression of myocardial contractility (23). Hypovolemia and opioid use potentiate the hypotensive effects of propofol. Bradycardia occurs occasionally possibly due to drug action on the conduction system or autonomic nervous system (24). However, propofol rarely results in severe bradycardia or conduction abnormalities, but should be used with caution with other vagotonic drugs such as opioids. Propofol's effects on the respiratory system include a reduction in minute ventilation, tidal volume and functional residual capacity (4,25). Since propofol is a respiratory depressant, caution should be used when it is administered with other agents, especially opioids, as apnea will occur in virtually all patients when these drugs are used concurrently (6). Propofol depresses pharyngeal reflexes and decreases jaw muscle tone, thus facilitating intubation, and may obviate need for paralysing agents during routine intubations (8,9). Propofol has little, if any, effect on liver or adrenal functions (10,15).

Propofol in the ICU

Propofol is an effective sedative agent for use in the ICU, especially for patients receiving mechanical ventilation. Propofol infusion in the ICU has been demonstrated to be safe and effective for patients requiring prolonged sedation (up to 5 days) during mechanical ventilation (10,26). Grounds *et al.* (26) compared propofol with midazolam for sedation in a group of 60 post-cardiac surgery patients, and showed that patients administered propofol generally recovered more rapidly from sedation. In this study, propofol patients regained spontaneous ventilation in an average of 9·5 min compared to 202 min for midazolam; times to extubation averaged 20 min for the propofol group and 237 min for the midazolam group.

Chamorro *et al.* (27) conducted a multicenter, randomised, prospective, non-blinded study comparing propofol with midazolam for sedation of patients in the ICU. The average duration of sedation was less for the propofol group (81 h) than the midazolam group (88 h). This study also demonstrated that propofol was a more effective sedative than midazolam for achieving patient synchrony with the ventilator. Patients administered propofol regained consciousness more rapidly than patients sedated with midazolam (27 min *vs.* 237 min).

An ideal drug for ICU sedation has been described by one author as one that: produces sedation without cardiovascular or respiratory depression; does not influence the metabolism of other drugs; is metabolised in a manner not dependent on hepatic or renal function; and has a short half-life without accumulation of the parent compound or its metabolites (28). Although no agent can simultaneously fulfill all of these ideal criteria, propofol has been proven useful in the critically ill population, especially in those patients with hepatic or renal failure. Also, rapid recovery of patients from sedation is important and, as shown in the studies noted above, may lead to easier extubation and, ultimately, shorter time spent on the ventilator.

Dosing and Administration

Dosing of propofol for mechanically ventilated ICU patients includes an initial bolus followed by a maintenance infusion. The recommended loading dose is 5–10 $\mu g\,kg^{-1}\,min^{-1}$ followed by an infusion rate titrated to the level of sedation. It is important to remember that propofol acts synergistically with midazolam in producing sedation, and doses may need adjustment if these drugs are used concurrently (29). Also, sedation should be discontinued in a manner similar to initiation to avoid anxiety and agitation which can occur when propofol is abruptly withdrawn.

Propofol may be administered through a peripheral vein on the dorsum of the hand or antecubital fossa, but pain on injection is common when these sites are used. However, since propofol is a lipid emulsion, it is preferable to administer it through a central vein to minimise irritation and damage to peripheral veins (15). Since the lipid vehicle has been shown to support bacterial growth, aseptic technique is mandatory (30–32). The manufacturer offers the following guidelines for administration: disinfection of the rubber stopper with 70% isopropyl alcohol before spiking with sterile intravenous tubing; avoiding excessive manipulation of the line designated for propofol infusion; and discarding the vial and tubing within 12 h after starting an infusion. Propofol contains no antimicrobials or preservatives so it is important that opened, unused propofol is discarded immediately (15,32).

Adverse Reactions

The safety profile of propofol is well established; however, there are adverse reactions with which clinicians should be familiar (Table 2). The most common adverse effect is pain on injection. As noted above, the central route of administration is preferred, but when propofol is given peripherally, pain occurs in 31% of patients when the dorsum of the hand is used and in 8% when a vein in the antecubital fossa is used. If a peripheral vein is used, the incidence of pain can be reduced by injecting 10 mg of 1% lidocaine 10 s before propofol, or mixing it with propofol immediately before infusion (6,15). Propofol should be used with caution in patients who are hypotensive, hypovolemic or hemodynamically unstable since, as noted above, the drug may cause profound hypotension. However, in most patients, such hypotension is transient and responds to a decrease in the drug infusion rate. Furthermore, the drug should be avoided in patients who are not intubated and mechanically ventilated, due to its potential for respiratory depression and blunting of airway reflexes. Propofol should not be administered to pregnant or lactating patients since there are no well-controlled human studies in these groups. Adverse reactions on the cardiac and respiratory system include hypotension, bradycardia and respiratory depression, and are discussed in the section of pharmacodynamic properties.

Neuroexitatory events have been reported during propofol use, and include tremor, twitching and hiccups (15). Opisthotonos, a tetanic reaction in which the spine and extremities are hyperextended with the body resting on the head and heels, has occurred with propofol and is felt to be due to tolerance to GABA-induced central nervous system inhibition. Most cases of opisthotonos, however, occurred in conjunction with fentanyl during surgical procedures, and only two cases have been reported when propofol was used alone (33). Hallucinations have been rarely reported in association with propofol use (34).

Anaphylaxis related to propofol has been reported, but it has been difficult to determine whether hypersensitivity is due to propofol or the lipid vehicle (35–37). One case report described a patient who experienced anaphylaxis to propofol and had a

TABLE 2. Adverse effects associated with propofol

Cardiovascular	Respiratory	Neurologic
Hypotension	Respiratory depression	Tremor
Bradycardia	Decreased airway reflexes	Twitching
	Enhanced CO_2 production	Hiccups
		Opisthotonus
Metabolic	**Miscellaneous**	
Hypertriglyceridemia	Injection pain	
Lactic acidosis	Anaphylaxis	
	Sepsis	
	Green urine	
	Nausea/vomiting	
	Pancreatitis	
	Hives	

positive intradermal test to propofol solution, indicating that the drug itself may be responsible for anaphylaxis, although reaction to the lipid solution could not be excluded (37). Localised histamine release has been postulated to account for a patient who experienced a wheal-and-flare response at the site of propofol infusion (38). As noted previously, propofol should be avoided in patients with known egg hypersensitivity as the vehicle contains 1·2% egg phosphatide.

Prolonged infusions of propofol in the ICU may increase carbon dioxide (CO_2) production since the emulsion contains 0·1 g fat (1·1 kcal) ml^{-1}. Excessive CO_2 levels may make weaning from mechanical ventilation difficult (39,40). The lipid content of the emulsion vehicle also increases serum triglyceride levels when infusions are prolonged (7–10 days). Blood specimens have been reported to be lipemic in children sedated with propofol as early as 2 days after initiation (41). Serum triglyceride and cholesterol levels in adults generally increase 3 days after commencing propofol, with triglyceride levels occasionally reaching four times normal (41,42). However, one study demonstrated no adverse effects related to a 3-day propofol infusion and noted no significant increase in serum lipid concentrations (43). Pancreatitis is a well-known complication of hypertriglyceridemia and remains a theoretical possibility with prolonged infusions. Serum lipid profiles should be monitored closely if propofol is continued past 72 h, especially in patients with underlying hypertriglyceridemia. Pancreatitis has been recently reported in postoperative patients receiving propofol without other obvious predisposing factors, but was not conclusively shown to be due to hypertriglyceridemia (44,45). Pancreatitis definitively associated with propofol remains to be established.

Fatal metabolic acidosis has been reported in children receiving propofol for sedation (41,46). Most of these cases involved patients being sedated during mechanical ventilation for laryngotracheobronchitis, with death caused by cardiac arrest. The cause of metabolic acidosis in these patients was not determined. It was postulated, however, that the lipid emulsion in propofol may impair hepatic clearance of lactate and lead to lactic acidosis, although none of these patients had serum lactate measured (41). A case of lactic acidosis was recently reported that was temporally associated with propofol in a young patient ventilated for an asthma exacerbation who had no other predisposing factors for lactic acidosis (1). Further studies will be needed to determine if lactic acidosis is indeed associated with propofol. Propofol has not been reported to be associated with significant liver injury (47).

Sepsis occurring after infusion of contaminated bottles of propofol has been reported (31,32). Propofol supports growth of various micro-organisms including Gram positives, Gram negatives and *Candida albicans* (Table 3). Propofol has been shown to support bacterial growth, with and without the lipid vehicle (15). A recent outbreak of propofol-associated bacteremia in seven hospitals between 1990 and 1993 was reported. Bacteria isolated from these instances

TABLE 3. Micro-organisms linked to bacteremia with contaminated propofol

Candida albicans
Enterobacter agglomerans
Klebsiella pneumoniae
Moraxella osolensis
Serratia marcescens
Staphylococcus aureus

included *Staphylococcus aureus*, *C. albicans*, *Moraxella osloensis*, *Enterobacter agglomerans* and *Serratia marcescens* (32). Veber *et al.* (48) reported four patients with *Klebsiella pneumoniae* sepsis associated with propofol in patients undergoing anesthesia for surgery, from a common vial that had been open for more than 12 h before use. As noted above, strict aseptic technique must be followed when propofol is administered in the ICU.

Other less common adverse reactions to propofol include nausea, vomiting and green discoloration of urine. Propofol is a phenolic compound, a group of chemicals known for their tendency to cause green urine (49,50). A case of propofol abuse and dependence was reported (15). There have been two deaths reported from self-administered propofol overdose in doses of 400 and 1600 mg (51,52). Finally, the cost of propofol is extremely high, ranging from $380 to $1187 for a 24-h infusion, depending on the dose. Midazolam is priced similarly; however, lorazepam ranges from $36 to $379 for 24 h (4).

Summary

Propofol is a unique short-acting intravenous anesthetic agent that is useful for sedation of mechanically ventilated patients in the ICU. It has many attractive features including rapid onset and termination of action, safety in patients with renal and hepatic disease, and ease of administration and titratability. However, there are potential adverse reactions associated with the drug, most commonly hypotension. Other reported effects include bradycardia, central nervous system excitation, lactic acidosis, sepsis and green urine. Physicians who administer propofol to their patients should be familiar with these potential complications.

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